Mathematical Modeling and Prediction of Clinical Metastasis

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S. Benzekry

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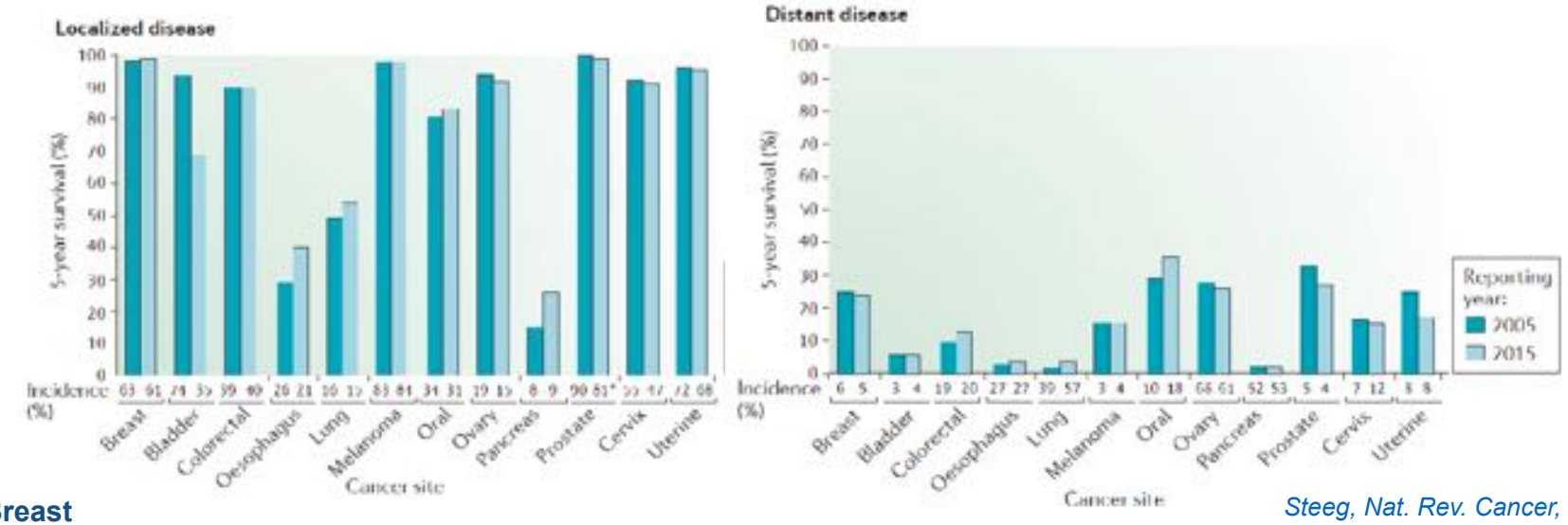
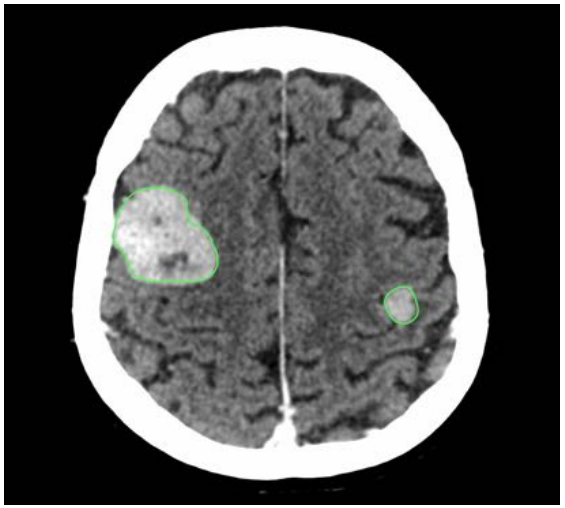
Metastasis (μετά = beyond, στάσιζ = place)

- Metastases are the **main cause of death** (>90%) from solid cancers *Lambert and Weinberg, Cell, 2017*



Steeg, Nat. Rev. Cancer, 2016

- **Breast**
  - 94% of cases are local or regional at diagnosis but 30% will relapse *Pollard, N Eng J Med, 2016*
  - Estimate the amount of **residual distant disease** at diagnosis in order to **personalize** the adjuvant (chemo)-therapy
  - Avoid unnecessary, heavy **toxicities**
- **Lung**
  - 57% of cases are metastatic
  - Decide whether to use **whole brain radiation therapy** or just (stereotactic) surgery
  - Avoid cognitive impairment of the patient



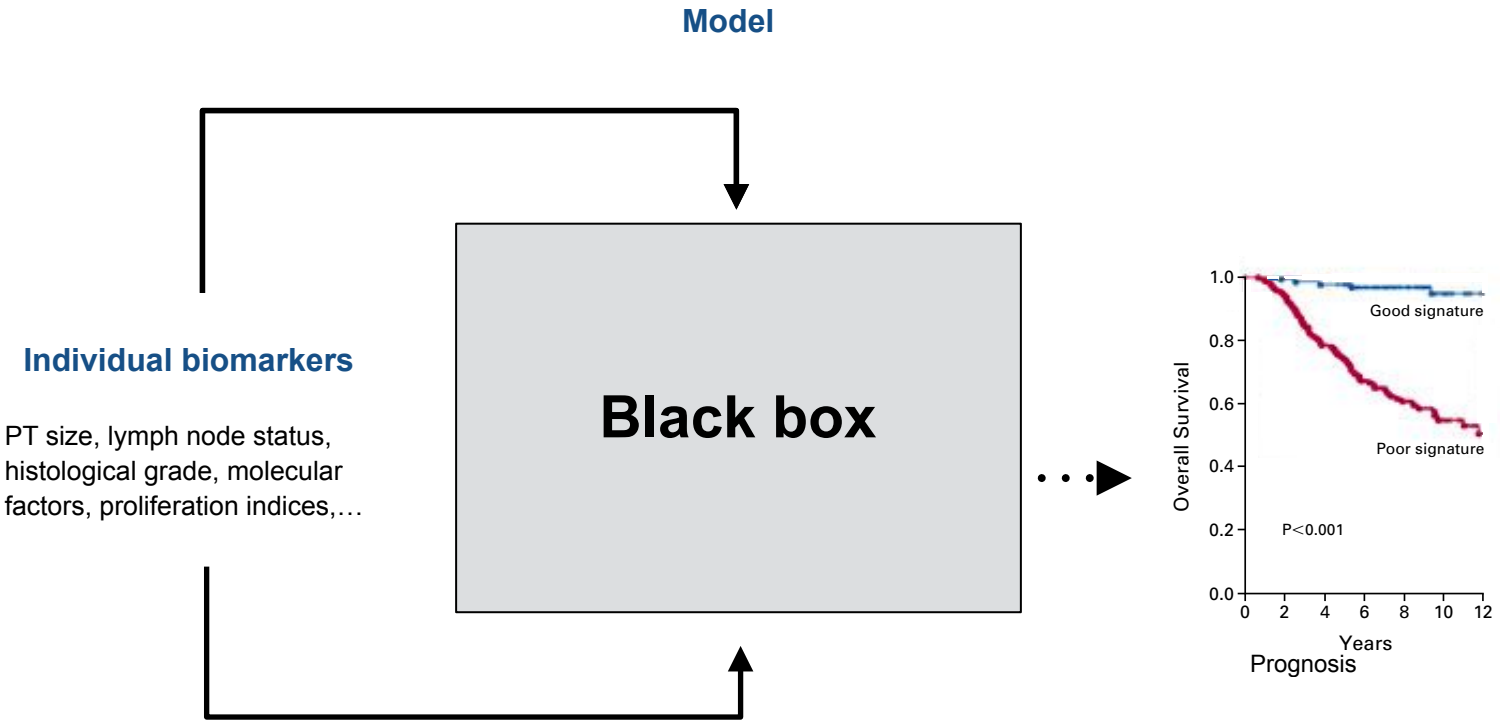
Institut Bergonié, Bordeaux

Some biological questions of interest to mathematical modeling

- **Minimal** model of metastatic dissemination and colonization able to reproduce the **systemic dynamics** of a solid cancer disease
- Investigate the relevance of several processes:
  - (early VS late event *Klein, Nat Rev Cancer, 2009*)
  - (metastases of metastases *Gundem et al., Nature, 2015*)
  - (dormancy *Chambers and Groom, Nat Rev Cancer, 2002*)
  - **tumor-tumor interactions**
  - (cancer-immune interactions)
  - **differential effect of therapy** *Ebos et al. (Kerbel), Cancer Cell, 2009*
  - ((pre-)metastatic niche *Peinado et al. (Lyden), Nature, 2005*)
  - systemic inhibition of angiogenesis *O'Reilly et al. (Folkman), Cell, 1990s*
  - (self-seeding *Norton, Nat Med, 2001*)

Metastasis: a forgotten major player in modeling

- The majority of mathematical modeling efforts in oncology are focused on (primary) **tumor growth**
- Existing models are based on a statistical, **biologically agnostic**, prediction of survival



Metastasis: a forgotten major player in modeling

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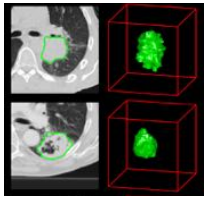
Clinical data

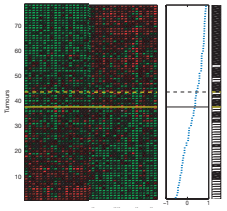
PT size, lymph node status, histological grade, molecular factors, proliferation indices,…

Imaging data (Radiomics)



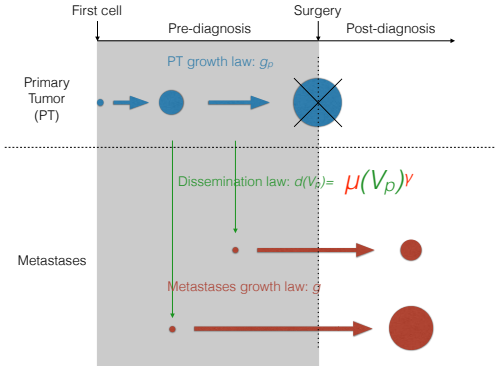
Aerts et al., Nat Commun, 2014

Molecular data (-omics)



van't Veer et al., Nature, 2002

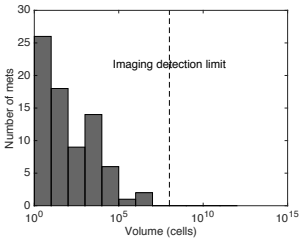
Biologically-based model



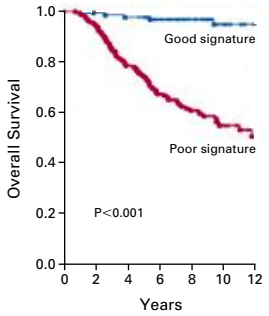
$$\frac{dV_p}{dt} = (\alpha_p - \beta_p \ln(V_p))\, V_p$$

$$\begin{cases} \partial_t \rho(t,v) + \partial_v \left((\alpha - \beta \ln(v))\, v \rho(t,v) \right) = 0 \\ g(V_0)\rho(t,V_0) = \mu V_p(t)^\gamma \\ \rho(0,v) = 0 \end{cases}$$

Prediction



Diagnosis



Prognosis

Simulation and individualization of therapy

Outline

1. Modeling the dynamics of **metastatic burden** in clinically relevant ortho-surgical animal systems

2. **Clinical** applications

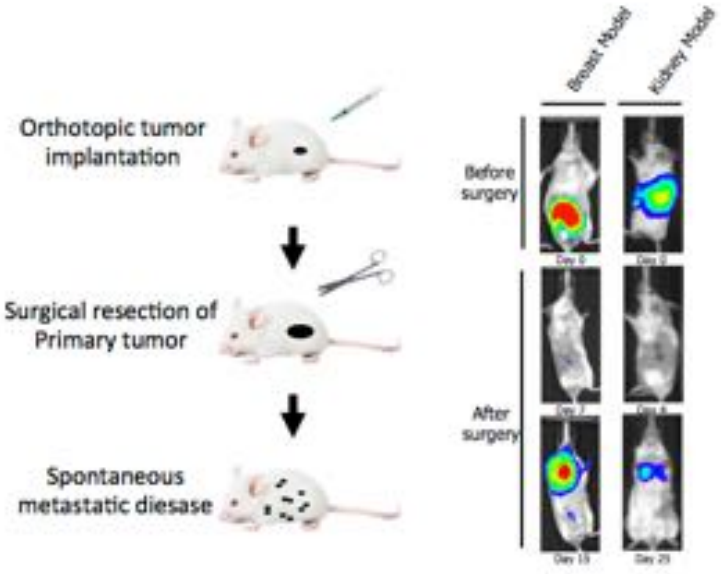
3. **Tumor-tumor interactions**

1. Modeling the dynamics of metastatic burden in clinically relevant ortho-surgical animal systems

Experimental data and questions

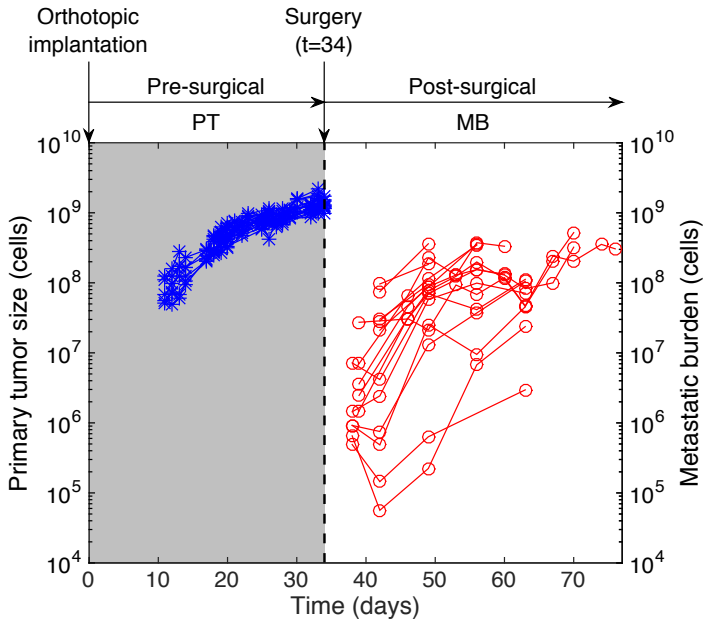
Data

- Clinically relevant ortho-surgical **animal models** of metastasis
- **Longitudinal** measurements of primary tumor size and total **metastatic burden**
- n > 400 animals

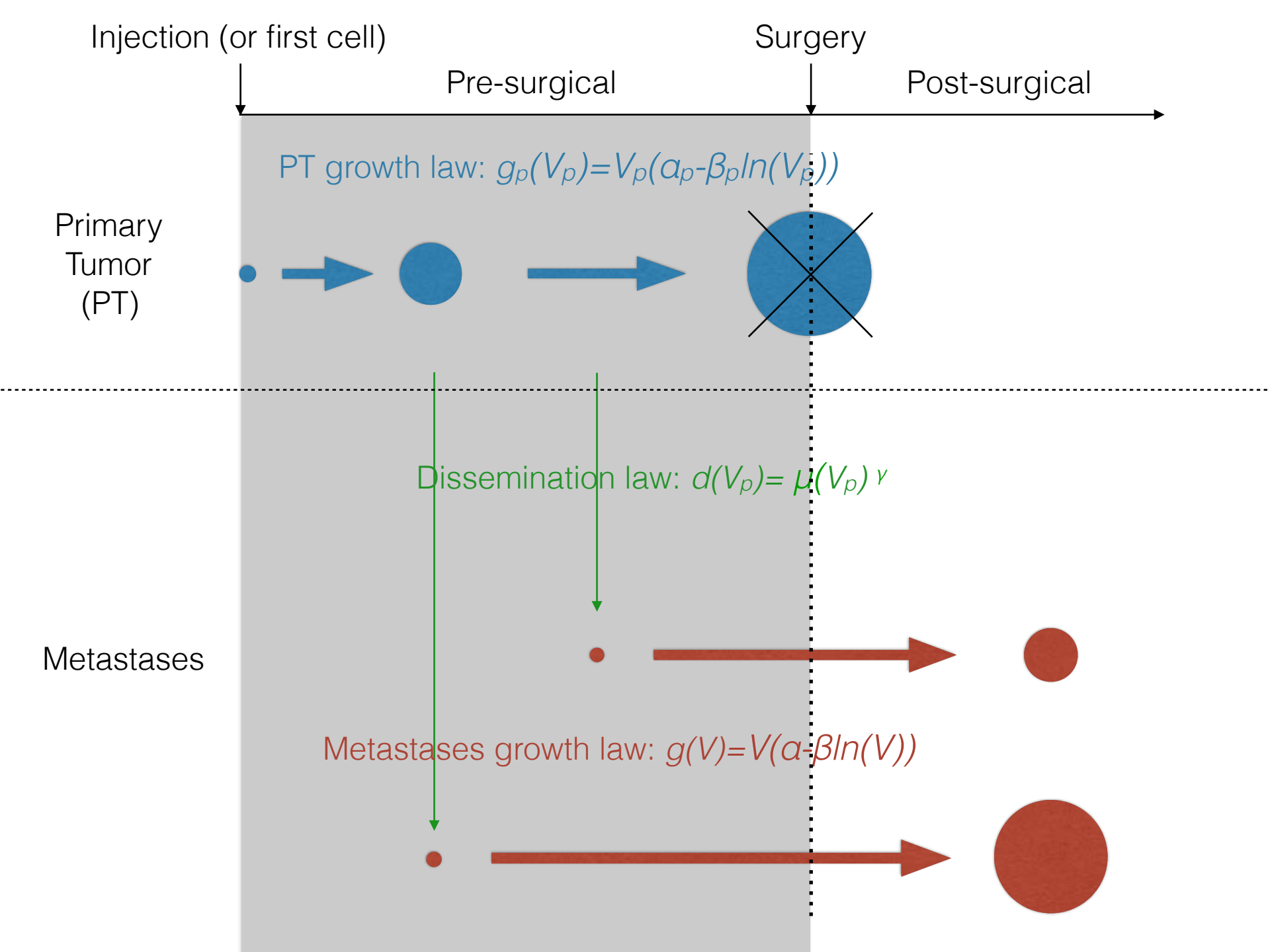


Questions

- Minimal model of metastatic development. **Dissemination** law? Differences between mets and primary tumor **growth**?
- Quantify the **inter-subject variability** of metastatic development
- What is the impact of the primary tumor size at surgery on metastatic development and survival?



Dr Ebos' lab, Roswell Park Cancer Institute


Injection (or first cell)
Surgery
Pre-surgical
Post-surgical
PT growth law: $g_p(V_p)=V_p(\alpha_p-\beta_p ln(V_p))$
Primary Tumor (PT)
Dissemination law: $d(V_p)=\mu(V_p)^{\gamma}$
Metastases
Metastases growth law: $g(V)=V(\alpha-\beta ln(V))$

Mathematical formalism

- Primary tumor V_p grows with rate g_p [size.day^{-1}]

$$\frac{d}{dt}V_p = g_p(V_p), \quad V_p(t=0) = V_i$$

- **Population** of metastases represented by a **density** ***ρ(t,v)*** [size^{-1}] structured in **size *v***

- Secondary tumors grow in size with rate *g(v)*

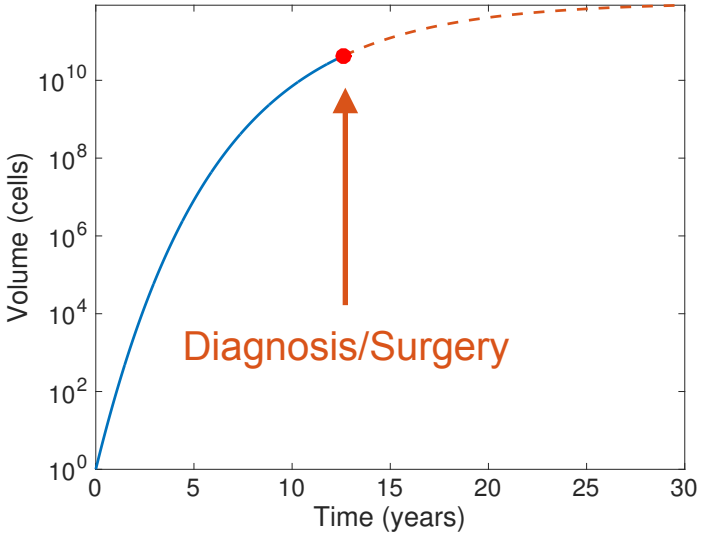
$$\partial_t \rho(t,v) + \partial_v(g(v)\rho(t,v)) = 0$$

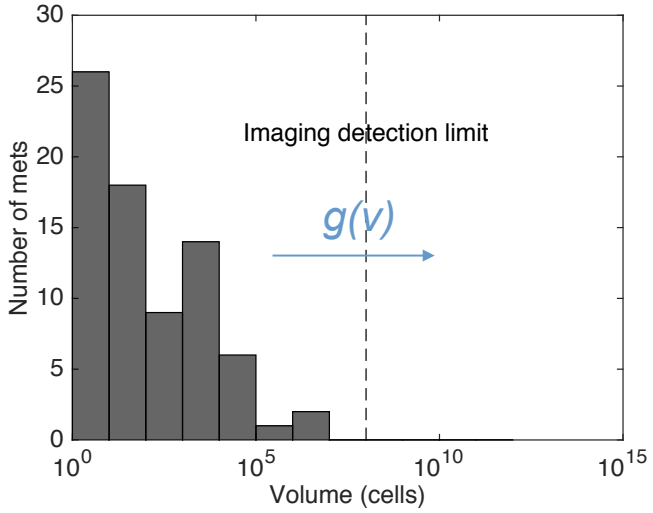
- They are spread by the PT with **dissemination rate** *d(V$_p$(t))* [day^{-1}]

$$g(V_0)\rho(t,V_0) = d(V_p(t))\left(+\int_{V_0}^{+\infty} d(v)\rho(t,v)dv\right)$$

⟶ fast computation of the metastatic burden

$$M(t) = \int_{V_0}^{+\infty} v\rho(t,v)dv = \int_0^t d\left(V_p(t-s)\right)V(s)ds$$





Iwata, Kawasaki, Shigesada, J Theor Biol, 2000

Statistical procedure: nonlinear mixed effects modeling

- Usual fitting methods consider each **time series independently**

$$y_i^j = M(t_i^j, \theta^j) + \varepsilon_i^j$$

MLE →

$$\hat{\theta}^j = \min_{\theta^j} \sum \left(y_i^j - M(t_i, \theta^j)\right)^2$$

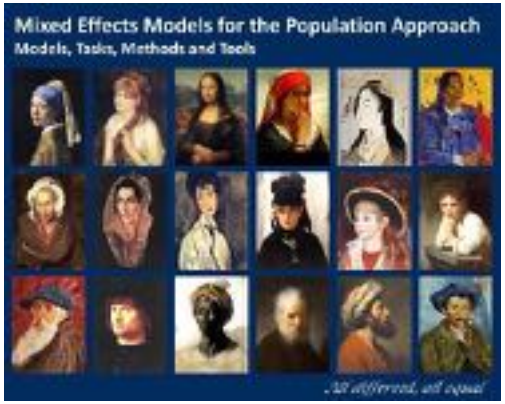
Individual $1 \leq j \leq N$

Time t_i

- When only sparse data are available from subjects in the same **population**, one can fit **parameters distribution** all-in-once

$$y_i^j = M(t_i^j, \theta^j) + \varepsilon_i^j$$

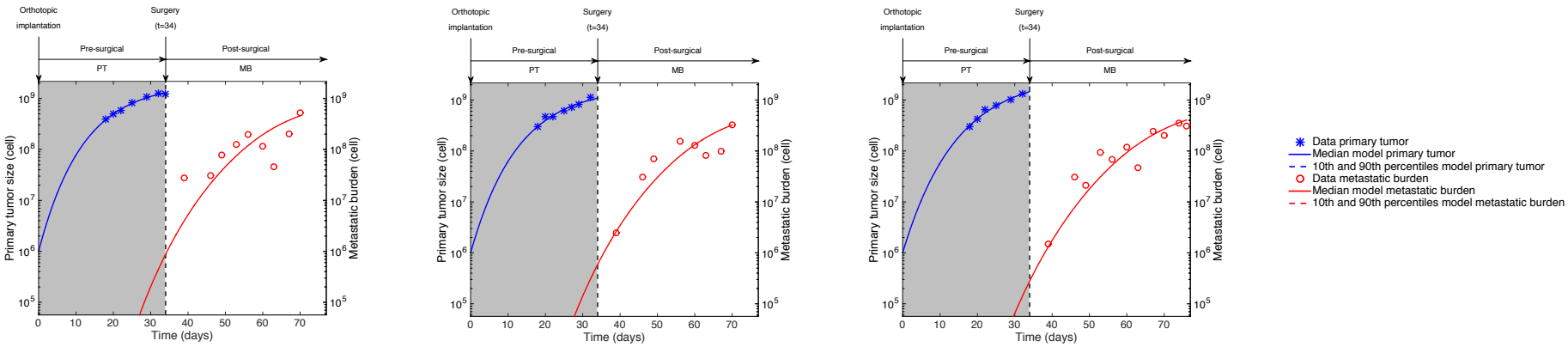
$$\theta^1, \ldots, \theta^N \sim \mathcal{LN}(\theta_\mu, \theta_\omega), \quad \theta_\mu \in \mathbb{R}^p, \ \theta_\omega \in \mathbb{R}^{p \times p}$$



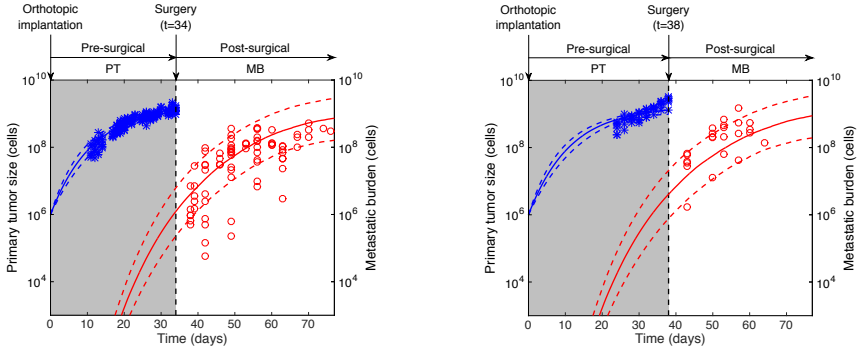
Lavielle,CRC press, 2014

- **Reduces the number of parameters from *pxN to p+p2***

The model fits at the individual and population levels



Fit **Prediction**



⇒ model with **same growth** for PT and mets was the most parsimonious

⇒ good **practical identifiability** (all rse < 30%)

⇒ parameter ***μ*** is a critical coefficient of inter-animal **variability** of metastatic potential (CV = 176%)

Nonlinear mixed-effects statistical model for inter-animal variability

$$\theta^i = \theta_{pop} + \eta_i, \quad \eta_i \sim \mathcal{N}(0, \omega^2)$$

Benzekry et al. (Ebos), Cancer Res, 2016

Differential effects of anti-angiogenic therapies between primary tumor and metastases

Cell PRESS

Cancer Cell
Report

Accelerated Metastasis after Short-Term Treatment with a Potent Inhibitor of Tumor Angiogenesis

John M.L. Ebos,[1,2] Christina R. Lee,[1] William Cruz-Munoz,[1] Georg A. Bjarnason,[3] James G. Christensen,[4] and Robert S. Kerbel[1,2,*]

Published online: October 31, 2014

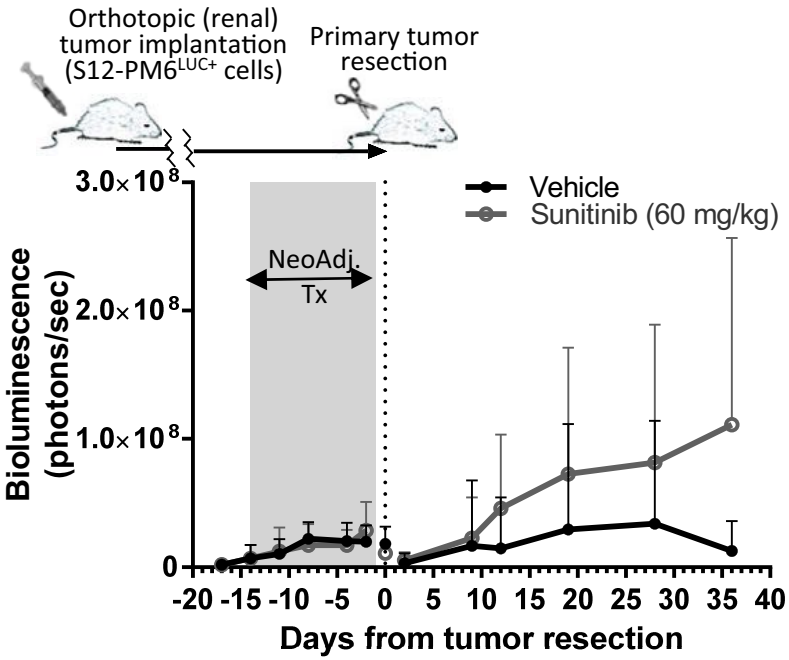
Research Article

TRANSPARENT PROCESS OPEN ACCESS

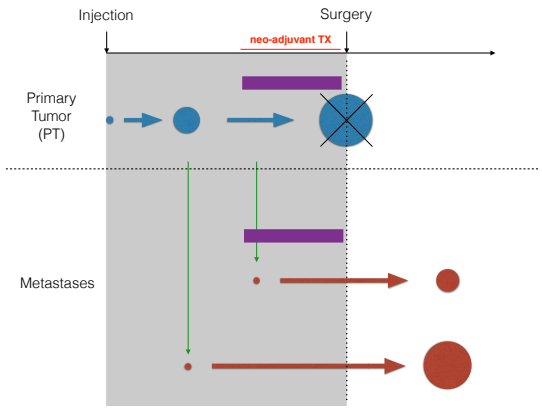
EMBO Molecular Medicine

Neoadjuvant antiangiogenic therapy reveals contrasts in primary and metastatic tumor efficacy

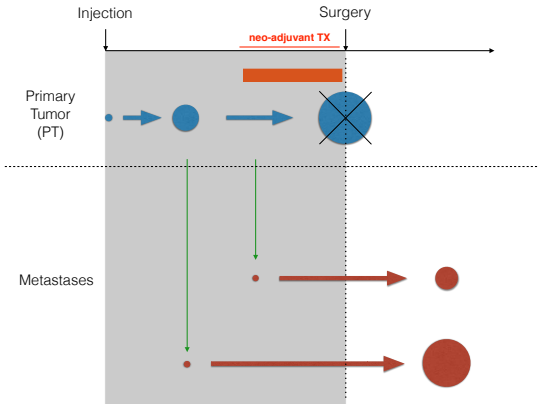
John M L Ebos[1,*], Michalis Mastri[1], Christina R Lee[2], Amanda Tracz[1], John M Hudson[2], Kristopher Attwood[3], William R Cruz-Munoz[2], Christopher Jedeszko[2], Peter Burns[2,4] & Robert S Kerbel[2,4]

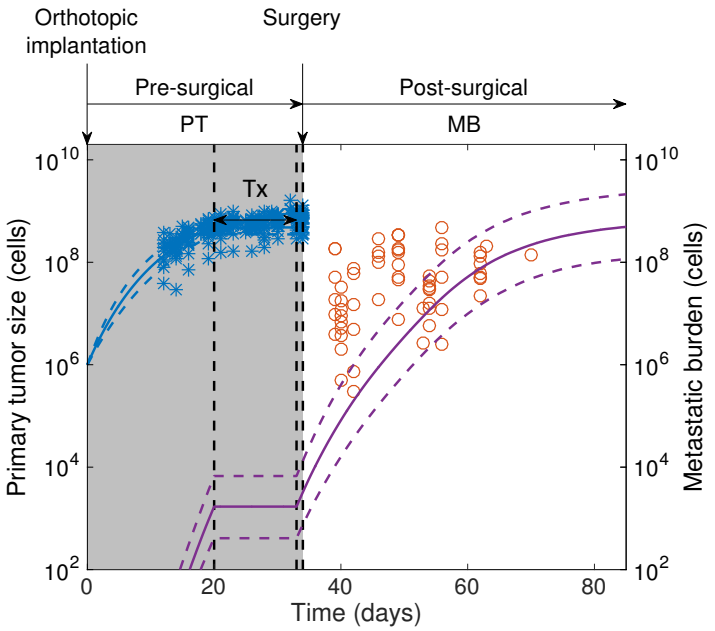


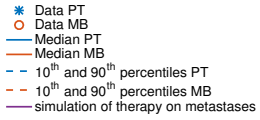
Testing hypotheses for Sunitinib effect

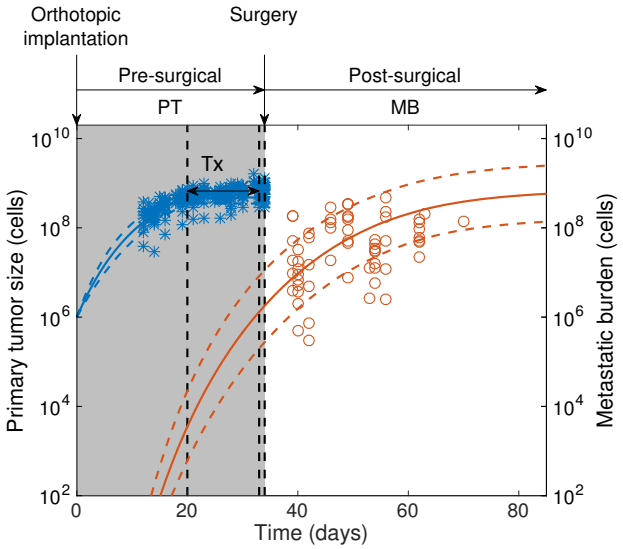


or

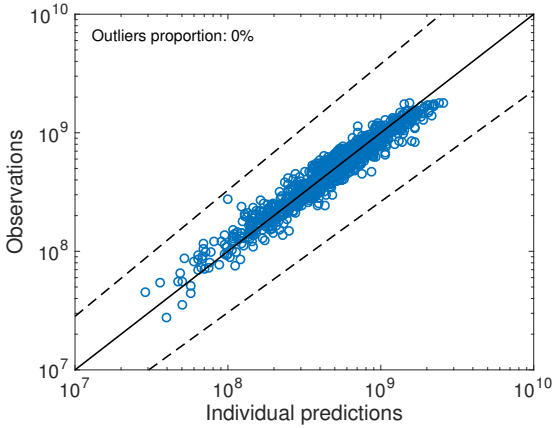


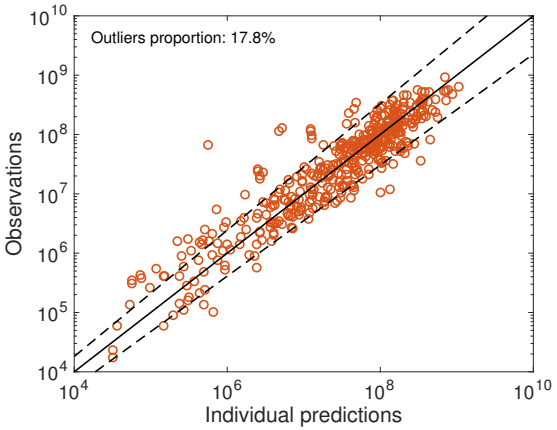


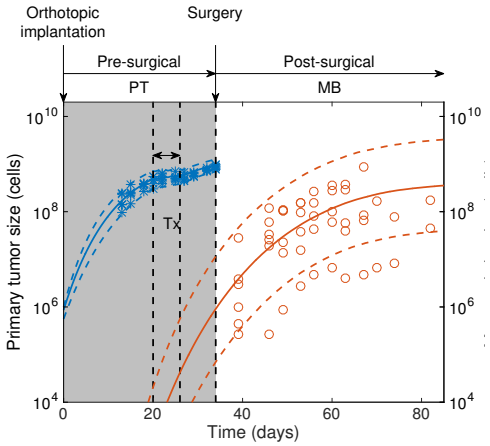




A validated model of metastatic growth with neoadjuvant Sunitinib therapy

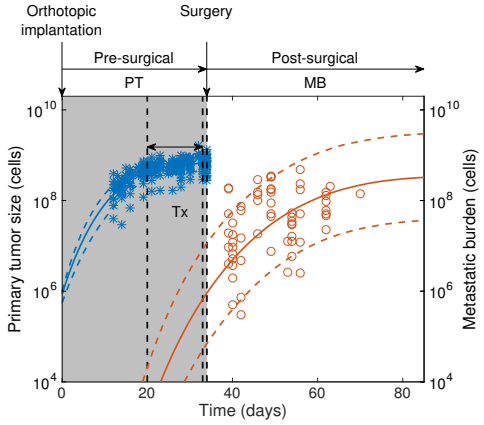






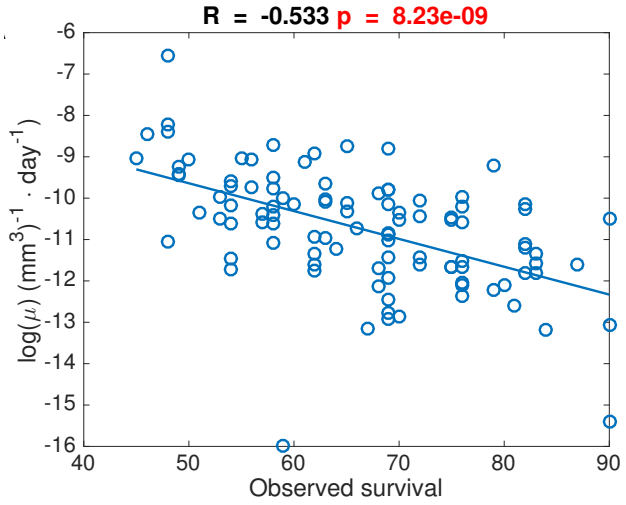
Su60(7D)

	Unit	Median value	CV (%)	r.s.e. (%)
μ	$cell^{-1} \cdot day^{-1}$	2.12e-11	1.48e+03	17.3
α	day^{-1}	1.94	18.1	2
β	day^{-1}	0.0911	19.7	2.21
k	$(mg/kg)^{-1}$	0.0372	32.1	6.34
k_e	day^{-1}	3.26 (fixed)	-	-

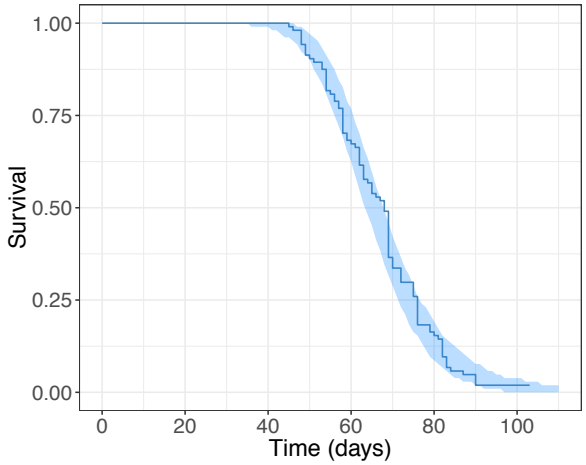


Su60(14D)

Survival model: μ as a covariate



Model fit



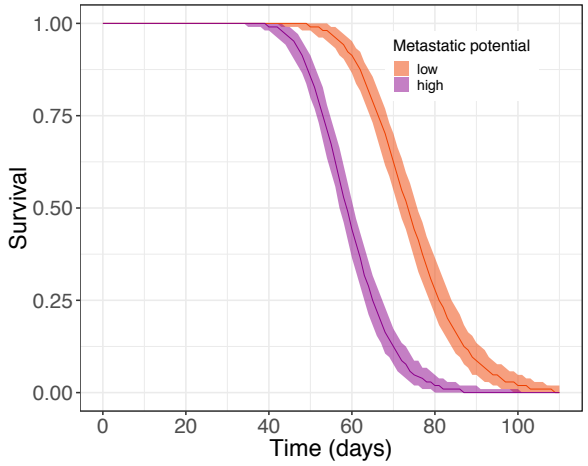
Nonlinear mixed-effects survival model

$$S^i(t) = \mathbb{P}(T^i \geq t) = e^{-\int_0^t h^i(s)ds}$$

$$h^i(t; T_e^i, s) = \frac{\frac{s}{T_e^i}\left(\frac{t}{T_e^i}\right)^{s-1}}{1 + \left(\frac{t}{T_e^i}\right)^s}$$

$$T_e^i = T_e^{pop} + \beta\mu^i + \eta^i, \quad \eta^i \sim \mathcal{N}(0, \omega)$$

Individual predictions of survival probability

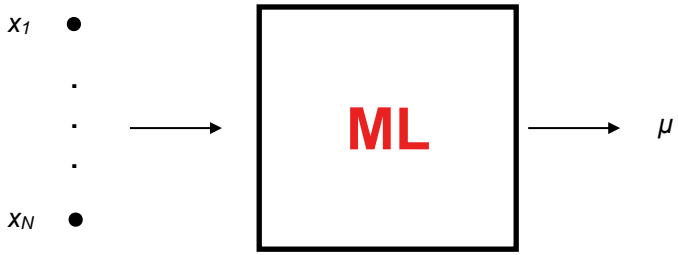


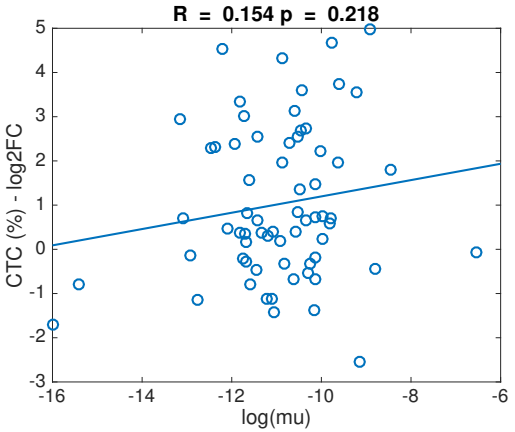
Nicolo et al. (Ebos, Benzekry), 2018, in preparation

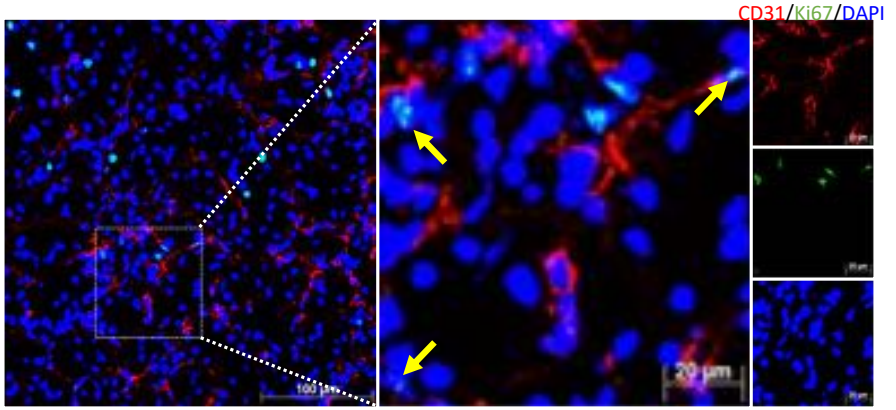
Trying to predict μ from biomarkers using machine learning

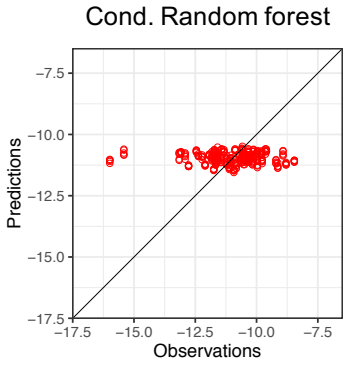
Biological measurements on multiple biomarkers

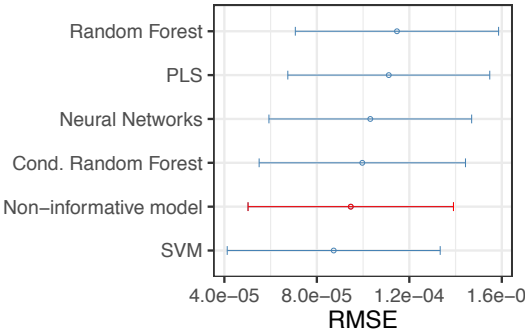
- Circulating tumor cells
- Proliferative (Ki67+) and endothelial cells (CD31+)
- Myeloid Derived Suppressor Cells (MDSCs)





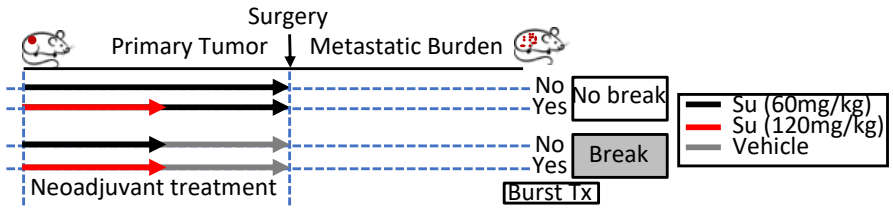


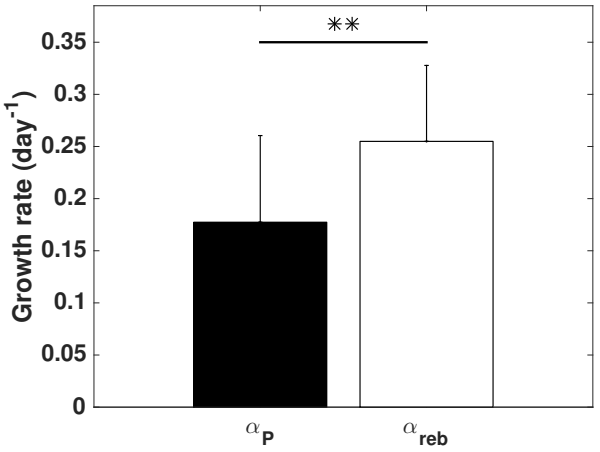


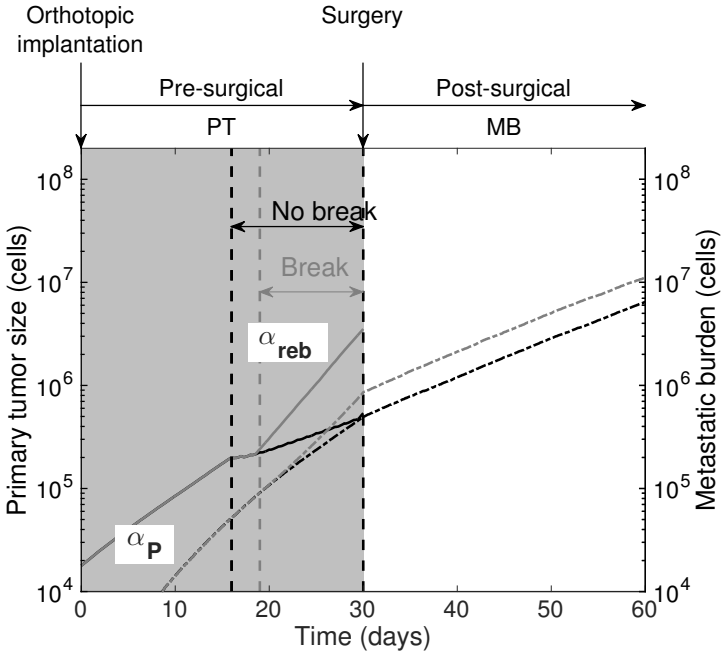


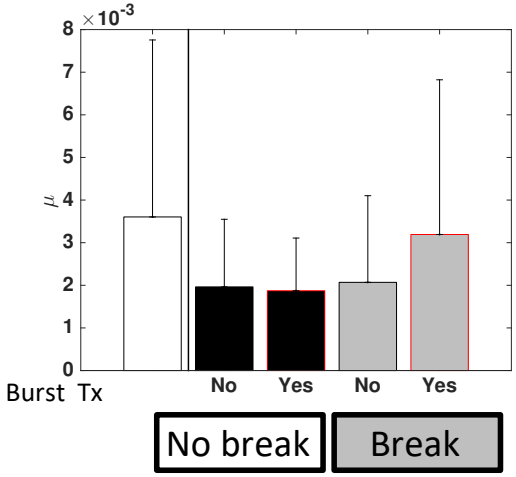
Nicolo et al. (Ebos, Benzekry), 2018, in preparation

Impact of treatment breaks









Mastri et al. (Benzekry, Ebos), 2018, in preparation

2. Clinical application

Metastatic relapse probability in a breast cancer clinical dataset

Diameter of PT (cm)	Prop. of relapse (Data)	Prop. of relapse (Model)
$1 \leq D \leq 2.5$	27.1	27.3
$2.5 < D \leq 3.5$	42.0	43.1
$3.5 < D \leq 4.5$	56.7	56.6
$4.5 < D \leq 5.5$	66.5	65.6
$5.5 < D \leq 6.5$	72.8	74.0
$6.5 < D \leq 7.5$	83.8	80.1
$7.5 < D \leq 8.5$	81.3	84.5

- 20 year follow-up of 2648 patients *Koscielny et al., Br J Cancer, 1984*
- **Assumptions**
  - (lognormal) distribution of μ for **inter-individual variability**
  - Doubling time from median values of the literature (7 months) *Coumans et al., BMC Cancer 2013*
  - Maximal reachable size = 10^{12} cells ≃ 1 kg *Klein, Nat Rev Cancer, 2009*
- Probability of developing a met = probability of having one at diagnosis

$$\mathbb{P}(\textbf{Mets}) = \mathbb{P}\left(\mu \int_0^{T_1} V_p(t) > 1\right)$$

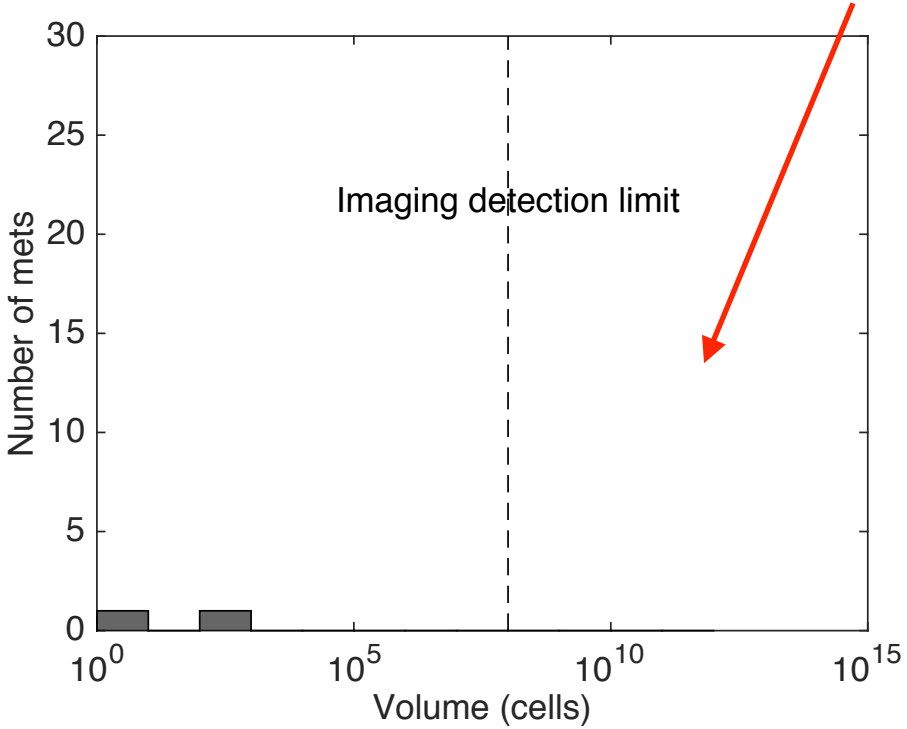
Benzekry et al. (Ebos), Cancer Res, 2016

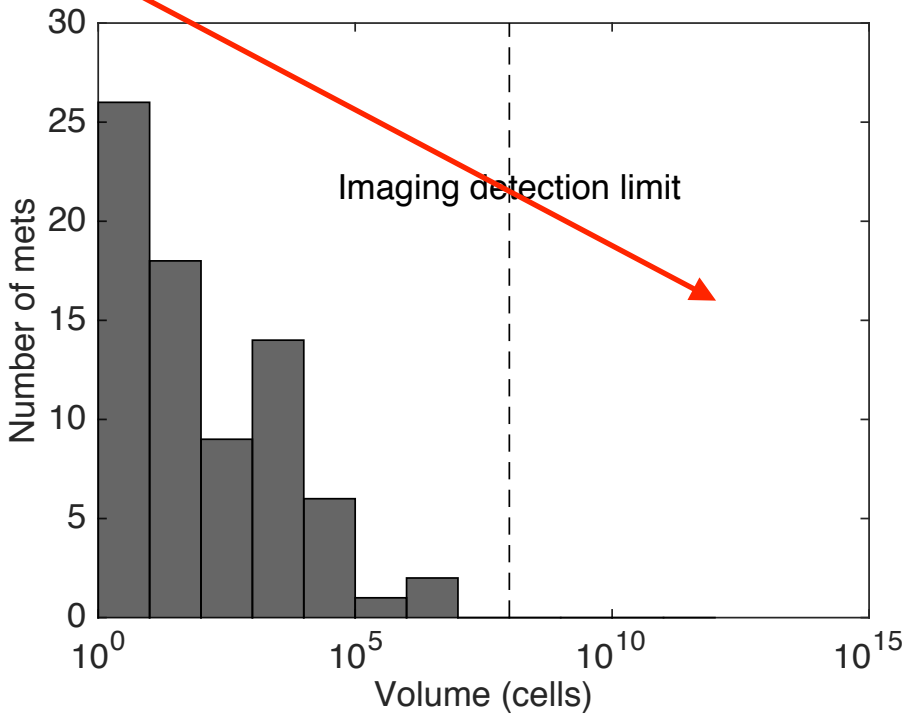
Diagnosis personalization

Virtual patient with median μ

Nothing visible

Virtual patient with large μ (90th prct)



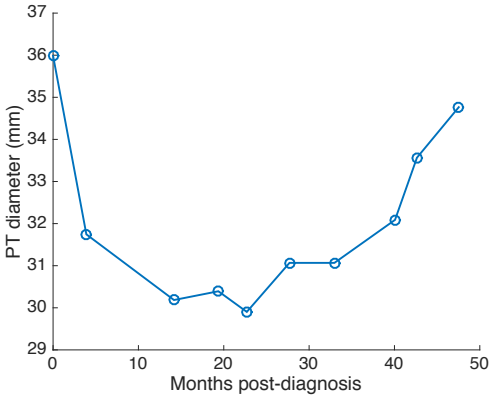


Breast cancer patient with primary tumor of 4.32 cm

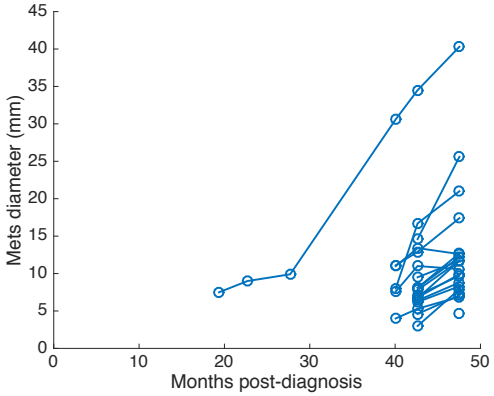
Benzekry et al. (Ebos), Cancer Res, 2016

Data of a NSCLC patient with brain mets

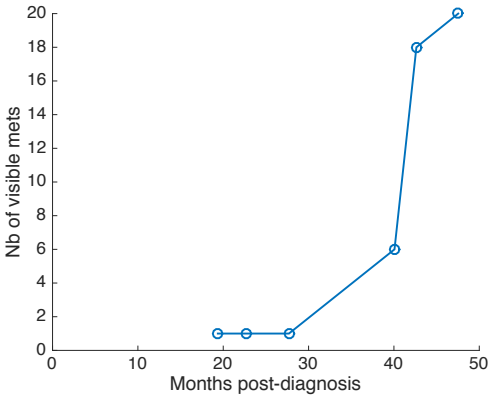
Primary tumor size



Metastases size

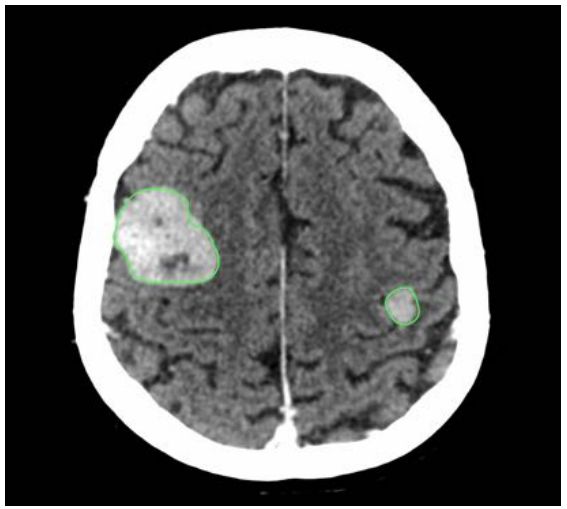


Number of visible mets



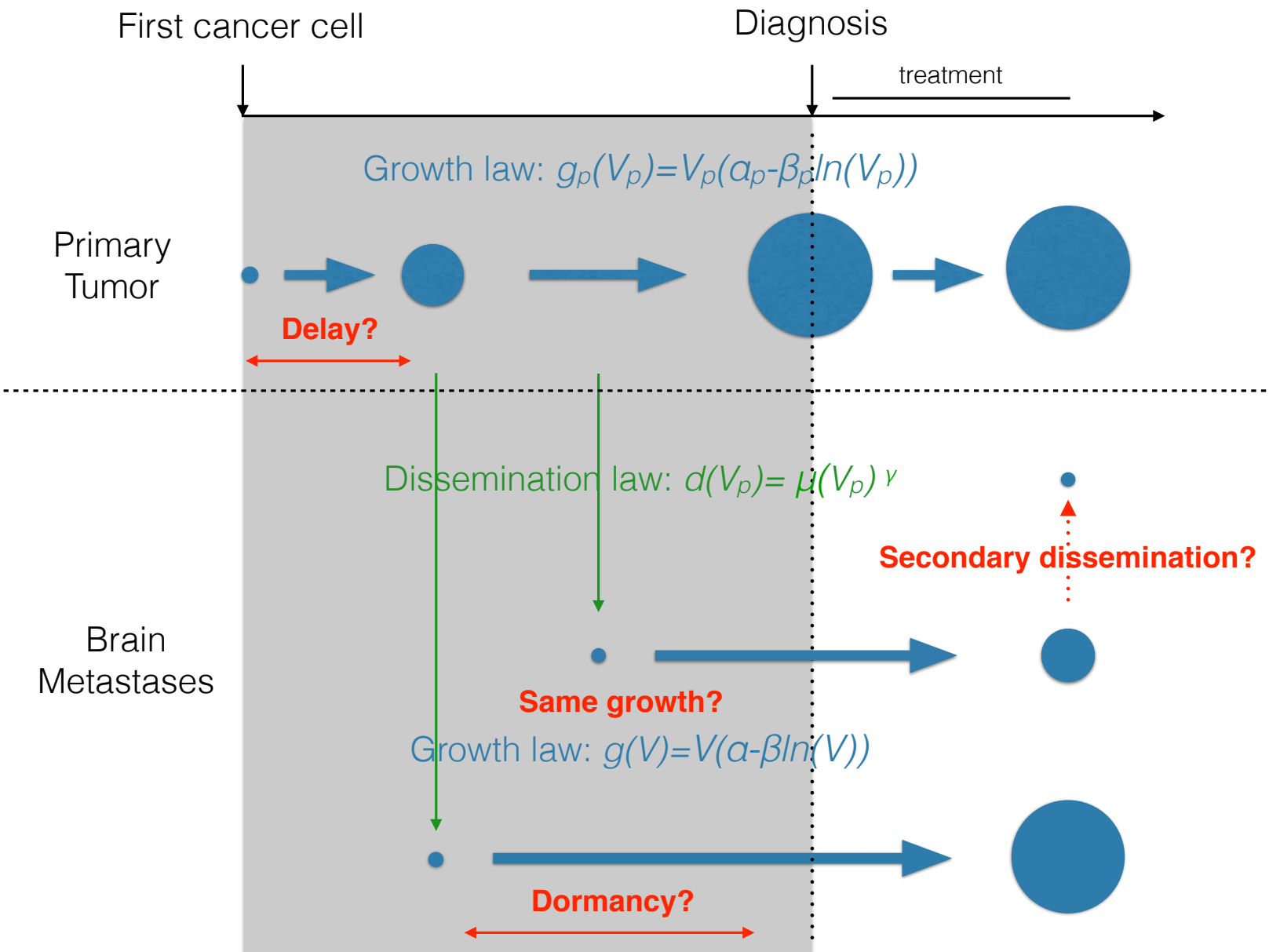
Lung CT

Brain CT scan

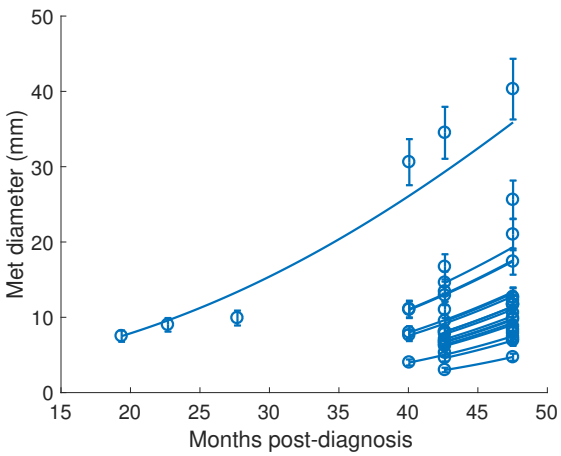


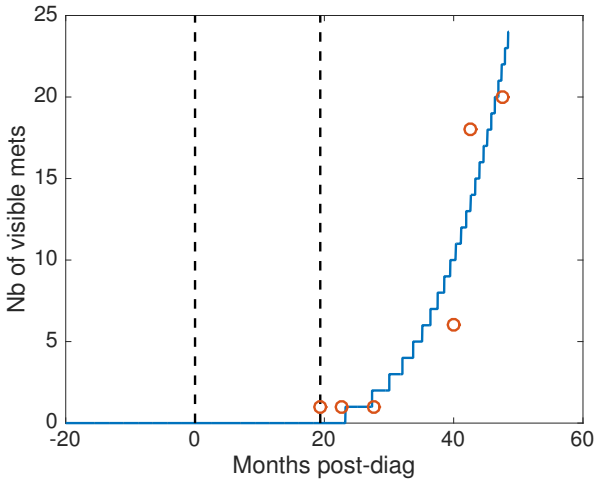
Institut Bergonié, Bordeaux, FR

Different biological scenarii



The model with dormancy could describe best the data





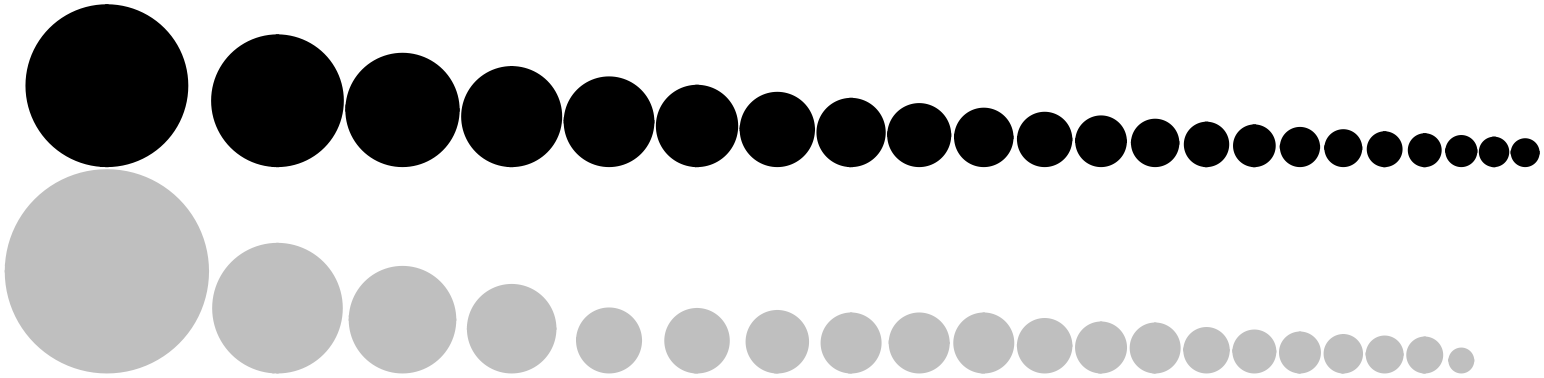
Objective function

Model	Patient 1	Patient 2
Base	5.51	2.53
Secondary	5.43	2.3
Delay	5.23	1.53
Dormancy	4.93	1.71
Diff. growth	4.95	1.79

Dormancy estimated to 133 days ± 4.2%

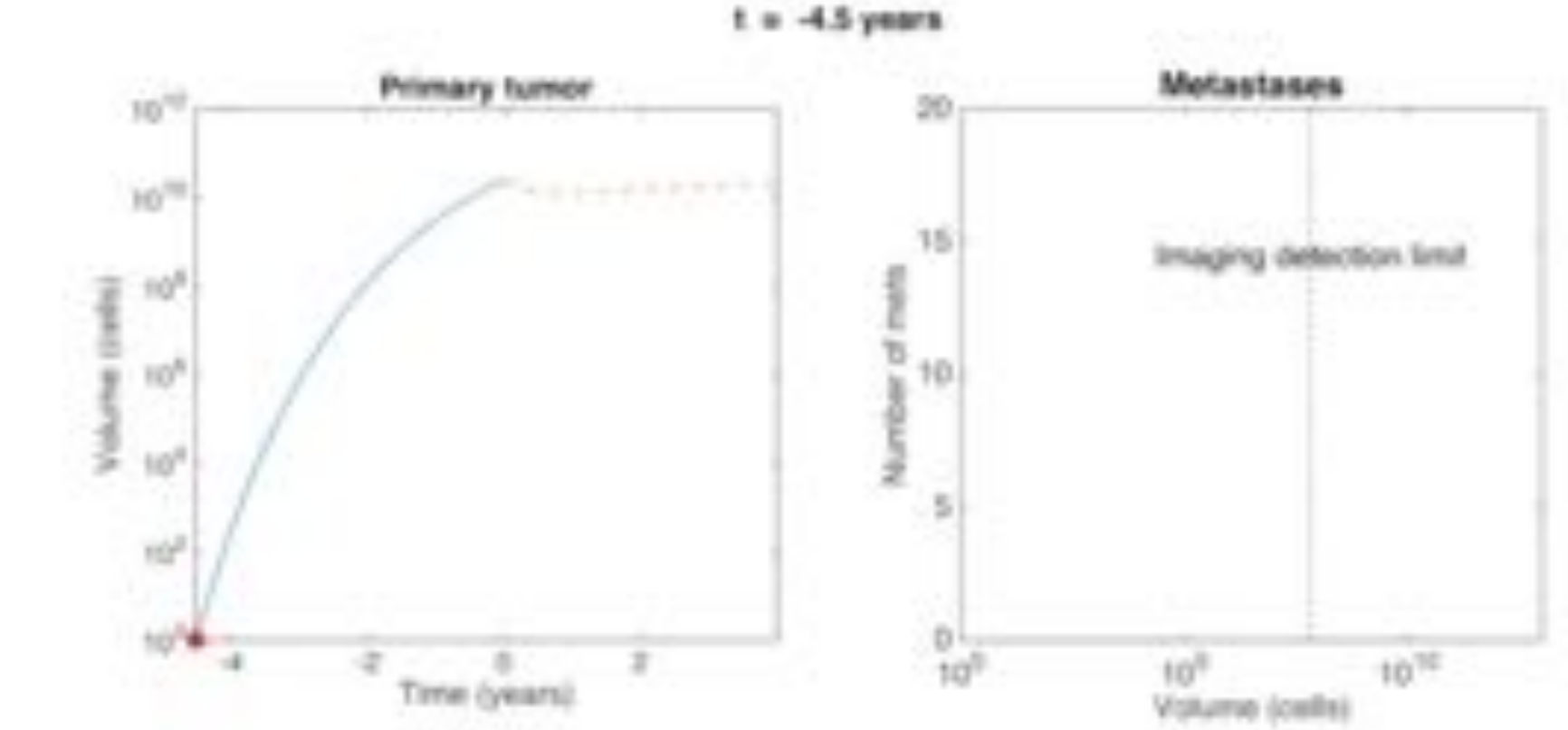
Model

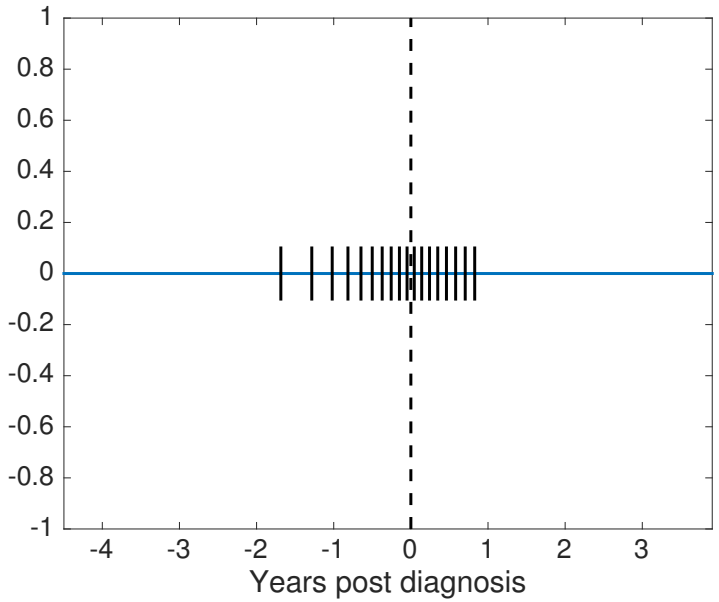
Data

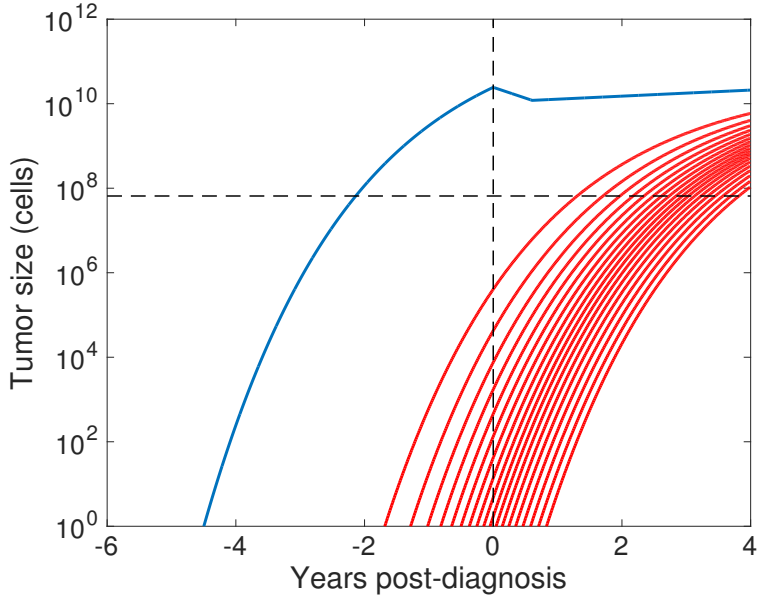


Bilous et al. (Benzekry), biorXiv, 2018

Bilous et al. (Benzekry), biorXiv, 2018

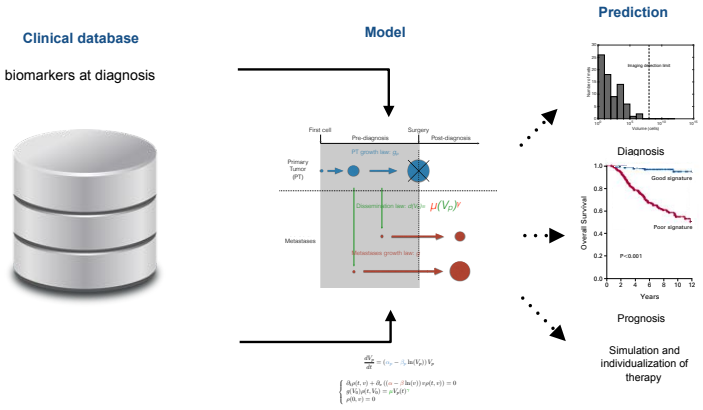

t = -4.5 years
Primary tumor
Volume (cells)
Time (years)
Metastases
Number of mets
Imaging detection limit
Volume (cells)


Years post diagnosis


Tumor size (cells)
Years post-diagnosis

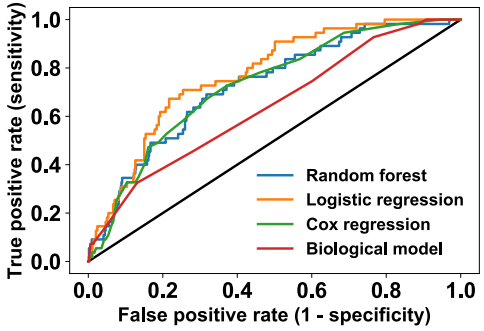
Current work: implementing the mechanistic model into a biostatistical model at the population scale

- Use the model for predictions of **time-to-relapse** and survival
- Implement clinical variables and biomarkers as **biologically meaningful** covariates
- Predict metastasis for localized **breast** cancer patients (~10% relapse at 5 years) to advise for **adjuvant therapy**



	AUROC	Accuracy	NPV	PPV
Random forest	0.727	87	91.7	22.5
Logistic regression	0.772	90.1	91	25
Cox regression	0.728	87.4	91.1	16.7
Bio-based	0.641	89.7	91.3	31.2

AUROC = Area Under the ROC curve, NPV = Negative Predictive Value
PPV = Positive Predictive Value



	p
tumor_size_clinical	0.00165
tumor_size_histological	0.4
grade	0.358
histology	0.0041
TNM_T	0.146
TNM_N	0.599
nb_invaded_ganglions	0.619
menopausal_status	0.000471
ER	0.543
PR	0.34
Ki67	3.09e-05
HER2	0.17
HER2_intensity	0.482
CK56	0.793
EGFR	0.016
VIM	0.226
ALDH1	0.674
CD24	0.894
CD44	0.397
E_cadherin	0.207
TRIO	0.0646
BCL2	0.727
age_at_diagnosis	0.0599
diagnosis_year	0.101
radio	0.276

Features selection based on Cox regression

Bergonié Institute, Bordeaux

M. Prague, SISTM, Inria Bordeaux

3. Tumor-tumor interactions: a dynamical study of concomitant resistance

Concomitant tumor resistance

- **Inhibition** of secondary **growth** by a primary mass
- Critical clinical implications in terms of **post-surgery metastatic acceleration**

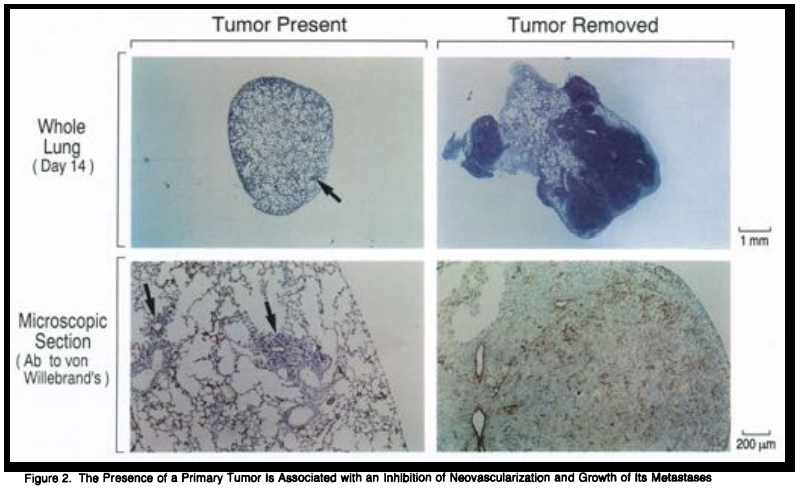


Figure 2. The Presence of a Primary Tumor Is Associated with an Inhibition of Neovascularization and Growth of Its Metastases

O'Reilly et al. (Folkman), Cell, 1994

Primary hypothesis: athrepsia (deprivation of **nutrients**)

Ehrlich, 1906

Non-immunogenic **systemic factors**

Dewys, Cancer Res 1972

Cytostatic circulating factor

Ruggiero et al., Br J Cancer 1985

Concomitant **immunity**

Bashford, 1908

CR occurs in **immune-deprived** mice

Gorelik, Int J Cancer 1981

Systemic inhibition of **angiogenesis**

O'Reilly et al. (Folkman), Cell 1994

Questions and experiment

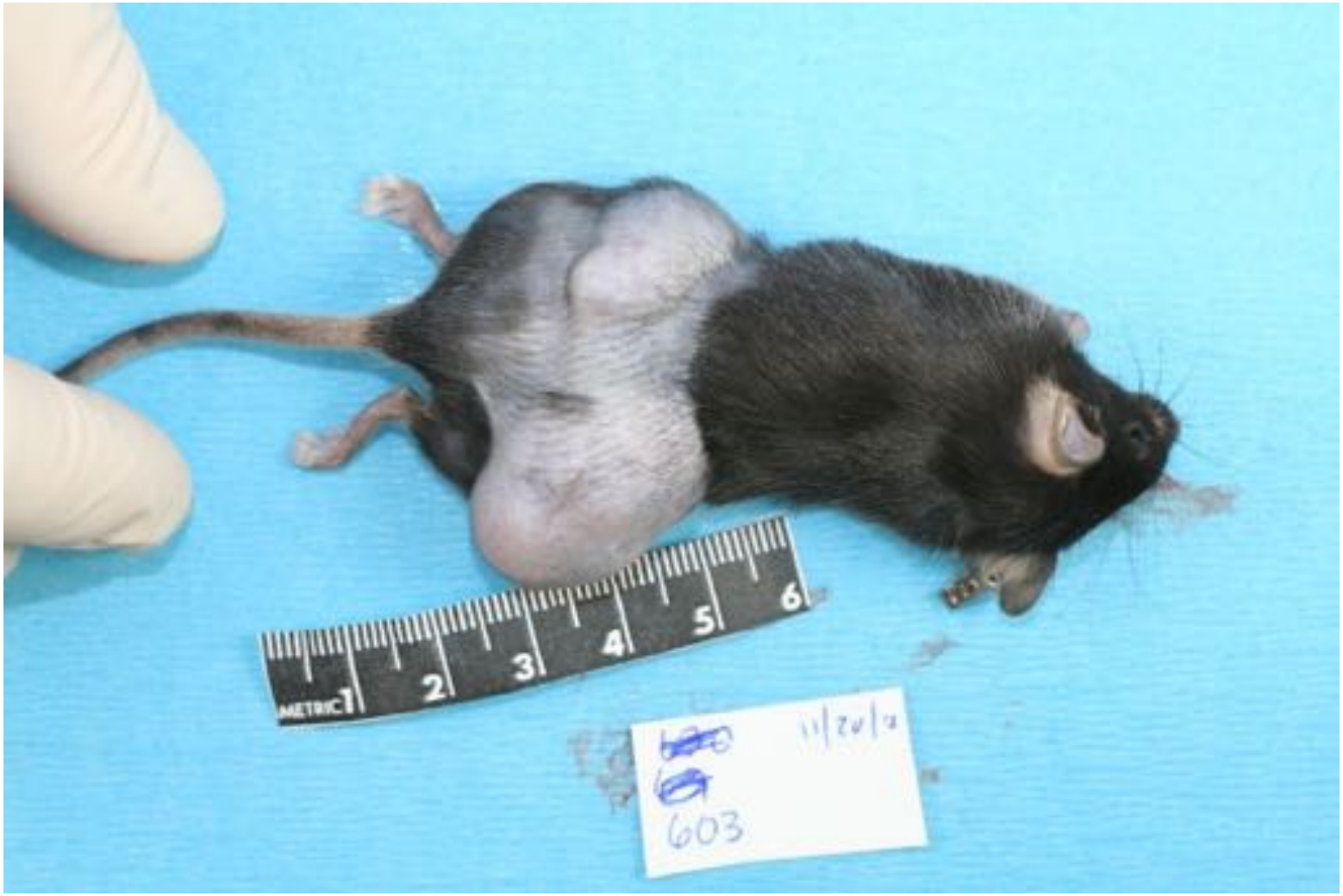
Questions

- **Quantitatively** distinguish between qualitatively valid **theories** of tumor-tumor interactions
- Establish and validate a **minimal model able to simulate tumor-tumor interactions**

Experiment

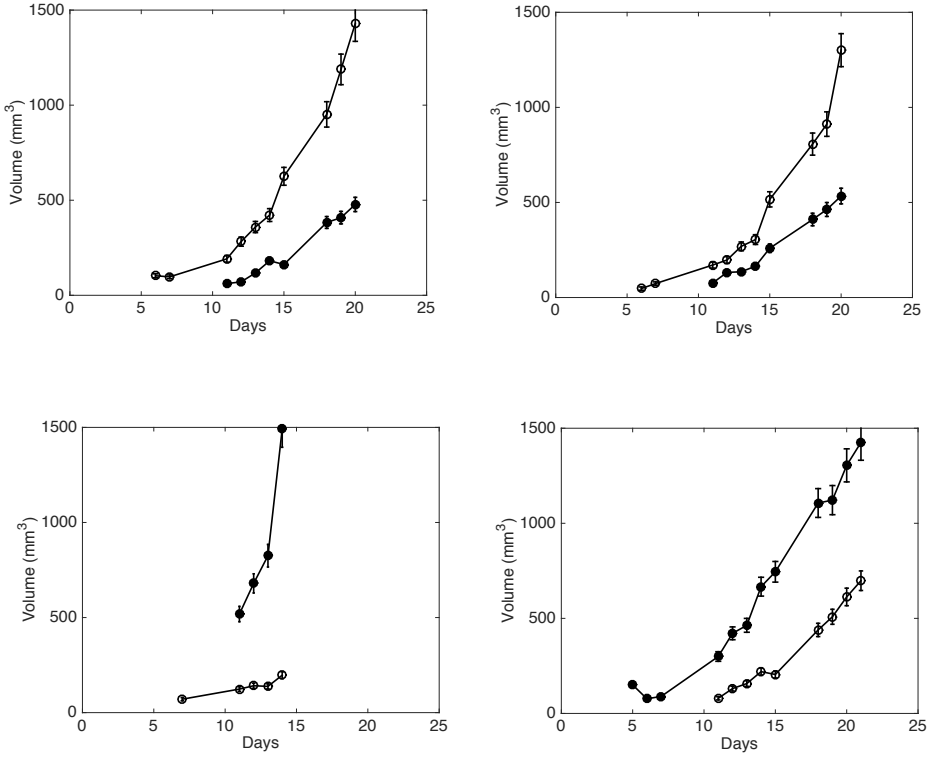
- Injection s.c. of **two tumors** of 10^6 LLC cells in C57/BL6 mice
- Two groups
  - Control: only one tumor
  - Group S: **simultaneous** injection of cells in two different sites

A mouse with two tumors

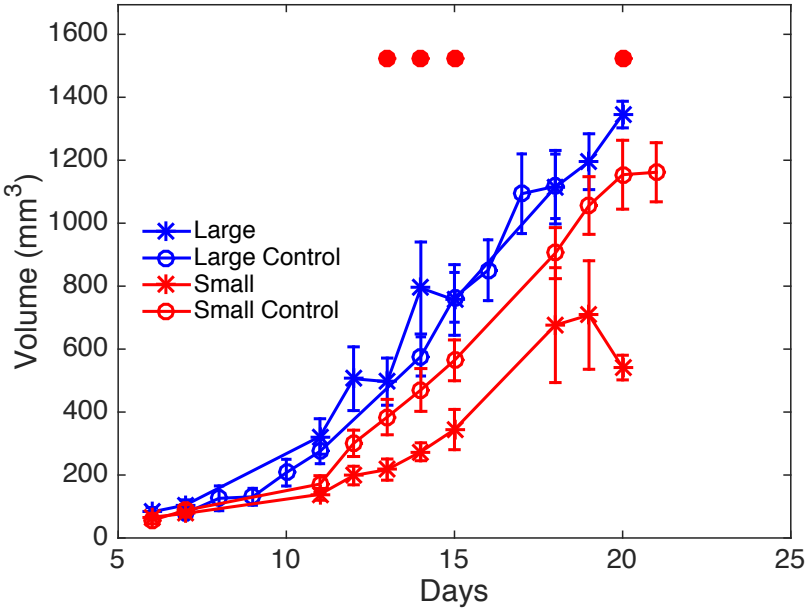


One tumor has normal growth and the other is suppressed

Individual growth kinetics



Small/Large in two-tumor bearing animals VS artificially paired small/large controls



Benzekry et al. (Hahnfeldt), Cancer Res, 2017

Two-tumors models

- Requirements:
  - **Symmetry:** same parameters for tumor 1 and tumor 2
  - Should resume to **single tumor growth** in the absence of the other tumor
- Main assumption for the difference between the two tumors: difference in **the initial take** ($V_{0,1}$ = 1, $V_{0,2}$ = 0.75)
- Difference in the growth kinetics should not result from difference in V_0
- Model selection (rejection) criteria: goodness-of-fit + parameter identifiability

Competition

$$\begin{cases} \frac{dV_1}{dt} = aV_1 \ln\left(\frac{K}{V_1+V_2}\right), & V_1(t=0) = V_{0,1} \\ \frac{dV_2}{dt} = aV_2 \ln\left(\frac{K}{V_1+V_2}\right), & V_2(t=0) = V_{0,2} \end{cases}$$

Angiogenesis inhibition

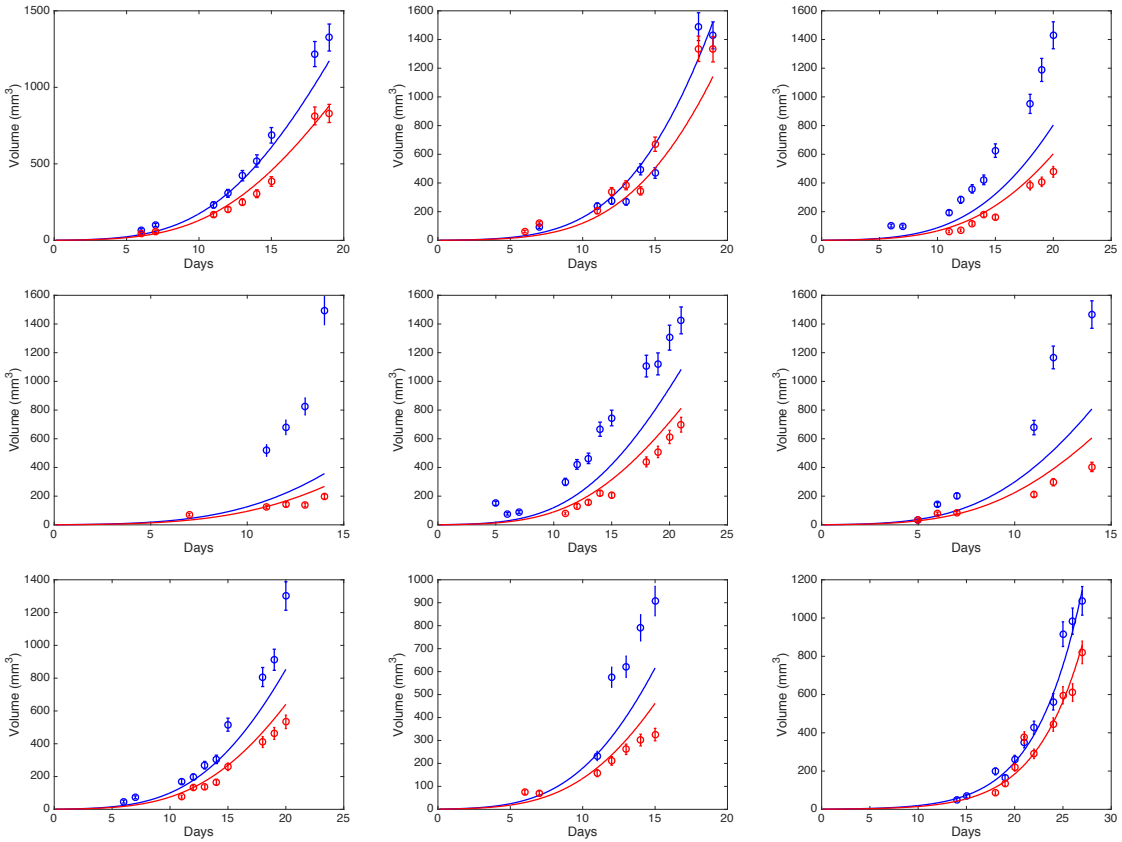
$$\begin{cases} \frac{dV_1}{dt} = aV_1 \ln\left(\frac{K_1}{V_1}\right), & V_1(t=0) = V_{0,1} \\ \frac{dK_1}{dt} = bV_1 - dV_1^{\frac{2}{3}}K_1 - eV_2 1_{K_1>K_0}, & K_1(t=0) = K_0 \\ \frac{dV_2}{dt} = aV_2 \ln\left(\frac{K_2}{V_2}\right), & V_2(t=0) = V_{0,2} \\ \frac{dK_2}{dt} = bV_2 - dV_2^{\frac{2}{3}}K_2 - eV_1 1_{K_2>K_0}, & K_2(t=0) = K_0 \end{cases}$$

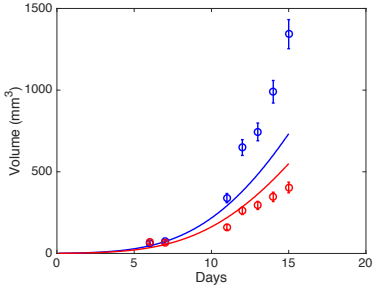
Proliferation inhibition

$$\begin{cases} \frac{dP_1}{dt} = \alpha P_1 - (\beta P_1 + \gamma(P_1+P_2))1_{P_1>0}, & P_1(t=0) = V_{0,1} \\ \frac{dQ_1}{dt} = \beta P_1 + \gamma(P_1+P_2), & Q_1(t=0) = 0 \\ \frac{dP_2}{dt} = \alpha P_2 - (\beta P_2 + \gamma(P_1+P_2))1_{P_2>0}, & P_2(t=0) = V_{0,2} \\ \frac{dQ_2}{dt} = \beta P_2 + \gamma(P_1+P_2), & Q_2(t=0) = 0 \end{cases}$$

Benzekry et al. (Hahnfeldt), Cancer Res, 2017

The competition model did not fit

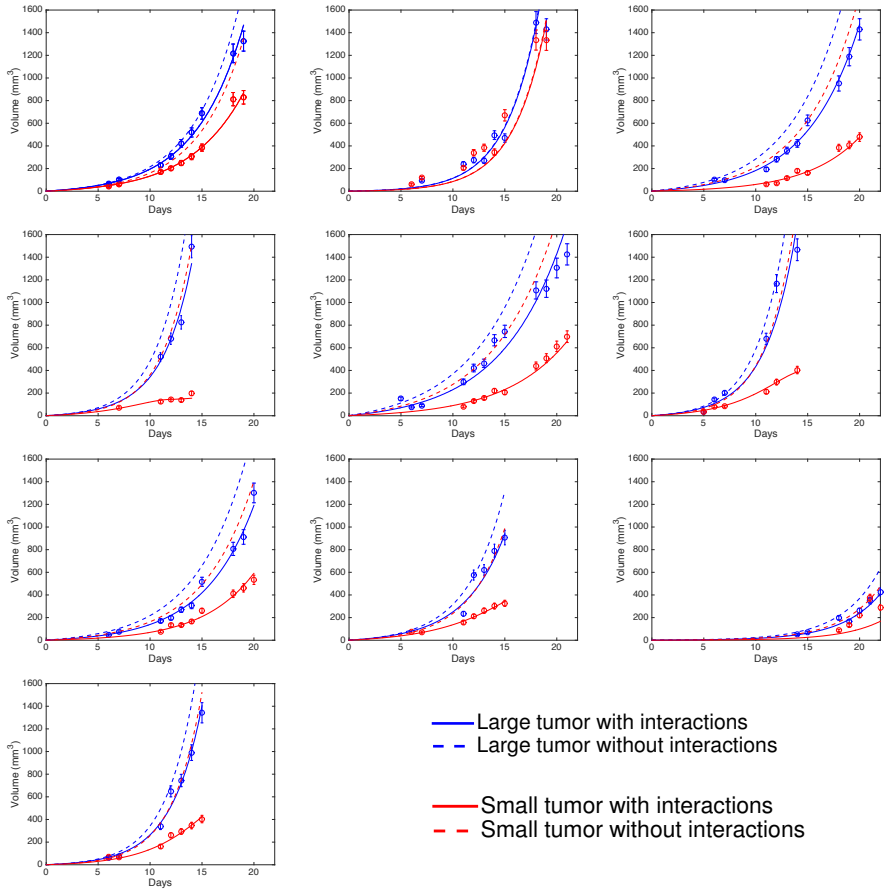


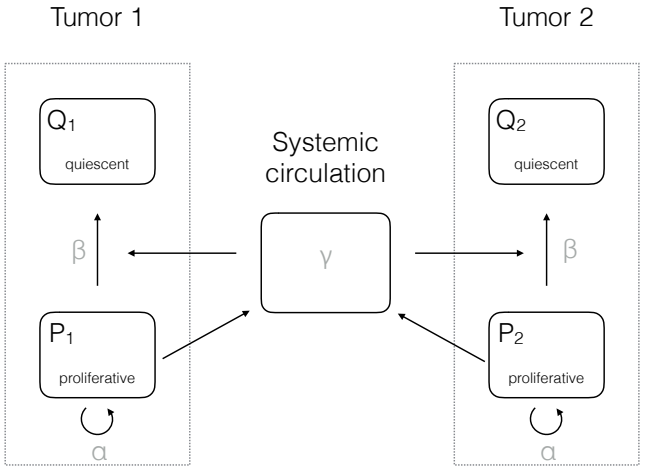


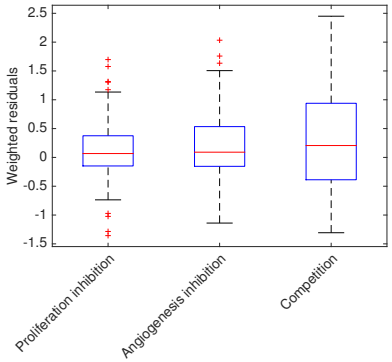
$$\begin{cases} \dfrac{dV_1}{dt} = aV_1 \ln\left(\dfrac{K}{V_1+V_2}\right), & V_1(t=0) = V_{0,1} \\ \dfrac{dV_2}{dt} = aV_2 \ln\left(\dfrac{K}{V_1+V_2}\right), & V_2(t=0) = V_{0,2} \end{cases}$$

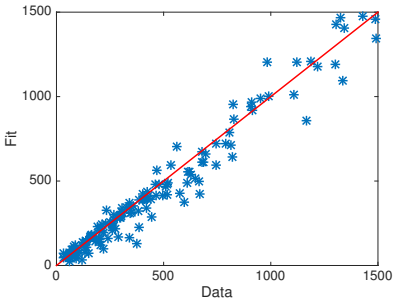
Benzekry et al. (Hahnfeldt), Cancer Res, 2017

The « inhibition of proliferation » model fitted best









Model	Par.	Unit	Median value (CV)	RSE (%)
Proliferation inhibition	α	day^{-1}	5.77 (67.4)	17.5
	β	day^{-1}	5.07 (49.3)	21.2
	γ	-	0.074 (2.69e+03)	2.47

Model	SSE	AIC	RMSE	R2	#
Proliferation inhibition	**0.204(0.0319 - 0.461)[1]**	**-14.2(-54 - -8.28)[1]**	**0.453(0.182 - 0.688)[1]**	**0.961(0.902 - 0.987)[1]**	3
Angiogenesis inhibition	0.336(0.154 - 0.772)[2]	-5.07(-27.5 - 5.67)[2]	0.588(0.4 - 0.891)[2]	0.957(0.645 - 0.986)[2]	3
Competition	0.666(0.141 - 2.2)[3]	0.71(-33.2 - 13.1)[3]	0.828(0.383 - 1.5)[3]	0.694(-0.0757 - 0.964)[3]	2

Conclusion

- A general modeling framework for **modeling metastases**
- Statistical nonliner **mixed-effects modeling** very useful for parameter estimations
- Simplified model (growth + dissemination) able to describe available clinically relevant **preclinical data** of dynamics of total metastatic burden
- **Same growth** for primary tumor and mets in breast animal model
- A **patient-specific key parameter μ** is critical in the quantification of patient-specific metastatic aggressiveness
- Could be clinically useful for guiding **adjuvant therapy** (chemotherapy/WBRT)
- Application to clinical data of **number and size** of brain mets suggested **dormancy** in NSCLC
- **Quantitative** exploration of classical theories for metastatic colonization and **tumor-tumor interactions**

Acknowledgements

Biology

- Preclinical data of ortho-surgical animal models of metastases

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✳P. Hahnfeldt

Center of Cancer and Systems Biology, Boston, MA, USA

Clinic

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✳F. Chomy

Bergonié Institute, Bordeaux, FR

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SMARTc team, CRCM, Inserm, CNRS, Marseille, FR

Modeling

✳C. Nicolò

✳D. Barbolosi

Thank you for your attention!